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1. Your reference

P022294GB: PNH/BRC

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2. Patent application number
(The Patent Office will fill in this part)

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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Cerebrus Pharmaceuticals Limited
Oakdene Court
613 Reading Road
Winnersh
Wokingham
RG41 5UA

Patents ADP number *(if you know it)*

07035181002.

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

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4. Title of the invention

CHEMICAL COMPOUNDS - III

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5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)*

83001

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6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body

   See note (d))

Yes

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Continuation sheets of this form	
Description	38
Claim*(s)*	4
Abstract	
Drawing*(s)*	1 + 1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Carpmaels + Ransford Date

Carpmaels & Ransford **23rd July 1999**

12. Name and daytime telephone number of person to contact in the United Kingdom **PAUL N. HOWARD** **0171 242 8692**

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CHEMICAL COMPOUNDS - III

The present invention relates primarily to neuroprotection and to the treatment of stroke and other cerebrovascular disorders.

Stroke and other acute brain injuries are major causes of mortality and morbidity in the adult population. Stroke is the third highest cause of death in major industrialised countries and the commonest cause of permanent disability. Each year, in the US and Europe, approximately 1 million people suffer an acute stroke. Between 25% and 35% of these patients die within the first three weeks, and of the survivors 25% to 50% will be totally dependant on family or institutional care for the rest of their lives. The incidence of stroke increases with age, roughly doubling with each passing decade, with 30% of persons aged over 65 years being affected.

The statistics for stroke translate into an annual incidence of 0.1 to 0.2% in the US and Europe, with the world-wide market for stroke estimated to be worth $3 billion in 1995 and projected to rise to $10 billion in 2005. There is an unmet medical need for a cytoprotective therapy for stroke.

No effective neuroprotectant therapy is presently available for cerebrovascular disorders. The only therapy currently licensed for the treatment of ischaemic stroke is Genetech's thrombolytic recombinant tissue plasminogen activator (Activase®, rtPA; Alteplase). Activase is indicated for the management of <u>acute</u> ischaemic stroke in adults for improving neurological recovery and reducing the incidence of disability. Treatment with Activase should only be initiated within 3 hours after the onset of stroke symptoms, and after exclusion of <u>intracranial</u> haemorrhage by a <u>cranial</u> computerised tomography (CT) scan or other diagnostic imaging method sensitive for the presence of haemorrhage.

The mechanisms underlying the irreversible brain damage which occurs following ischaemia are complex. Many classes of compounds are currently under investigation as treatments for cerebrovascular disorders. Acute intervention with both cytoprotective (neuroprotective) and other thrombolytic agents is undergoing active investigation.

Cytoprotective neuroprotective therapy includes drugs that act to prevent cell death dur ischaemia and reperfusion. These agents include calpain inhibitors, voltage-sensitive calcium- and sodium-channel antagonists, receptor-mediated calcium-channel antagonists [including *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) antagonists], glutamate-synthesis inhibitors, glutamate-release antagonists, γ-aminobenzoic acid (GABA) antagonists, 5-HT (serotonin) receptor agonists, gangliosides, antioxidants, growth factors, antiapoptotic agents, and antiadhesion molecules (Silver, B., Weber, J., Fisher, M., *Clin. Neuropharmacol.* **1996**, *19*, 101-128).

Excitotoxicity is a major determinant of neuronal death following the induction of cerebral ischaemia. Repetitive cell firing, persistent depolarisation and induction of supra-normal ionic flux across excitable membranes can initiate fatal cellular compromise *via* a variety of synergistic mechanisms during hypoxic excitotoxicity. Control of the state of excitability of neurons depends upon the net balance of excitatory and inhibitory influences acting on that neurone.

In general, the primary excitatory influence impinging on neurones is mediated by the glutamatergic system, whilst primary inhibition is frequently determined by GABAergic innervation, since the main endogenous inhibitory amino acid in mammalian brain is GABA. Thus increasing the inhibitory effect of GABAergic innervation, and decreasing the excitatory influence of glutamate, will reduce the net excitation of a neurone. Reducing excitation will reduce the consequences of energy depletion due to hypoxia and promote the ability of the neurone to survive hypoxic cerebral ischaemia.

Relatively few of the drugs currently under investigation as neuroprotectants for the treatment of stroke and other cerebrovascular disorders are modulators of the endogenous inhibitory amino acid, GABA.

One class of molecules which apparently possess neuroprotective properties is the GABA uptake inhibitors such as CI-966, which was shown to be effective in a gerbil ischaemia model utilising global cerebral ischaemia of 5 min. duration (Phillis, J.W., *Gen. Pharmacol.* **1995**, *26*, 1061-1064).

The benzodiazepine receptor agonist diazepam has been shown to possess some neuroprotective properties (Karle, J., Witt, M. R., Nielsen, M., *Brain Res.* **1997**, *765*, 21-29).

In rabbits with reversible spinal cord ischaemia, treatment with muscimol, a reference $GABA_A$ agonist, at 5 mg/kg significantly prolonged P_{50} time, where P_{50} represents the duration associated with 50% probability of resultant permanent paraplegia (Madden, K.P., *Stroke*, **1994**, *25*, 2271-2275).

Felbamate, an antiepileptic drug with *inter alia* GABA agonist properties, provided significant neuronal protection when administered both before and after ischaemia in all regions of the brain in the gerbil model of transient forebrain ischaemia. Protection was moderate when felbamate was used before ischaemia, but was highly significant when felbamate was given 30 min. after the insult. The structural protection with felbamate was very significant when used in the post-ischaemic period (Shuaib, A., Waqaar, T., Ijaz, M.S., Kanthan, R., Wishart, T., Howlett, W., *Brain Res.* **1996**, *727*, 65-70).

Piracetam is a derivative of GABA, and was the first commercially available nootropic drug. Although widely evaluated in the treatment of senile cognitive disorders and dyslexia, piracetam has also been assessed as a treatment for deficits associated with acute stroke. Data from a number of small, short term studies in patients treated within a few days of stroke suggest that piracetam is more effective than placebo for the treatment of functional deficits (Noble, S., Benfield, P., *CNS Drugs* **1998**, *9*, 497-511).

Some combination neuroprotectant therapies have been investigated in rodent ischaemia since the excitotoxic effects of glutamate can be blocked almost completely with GABA in cell culture, tissue slices, and in some animal models. On this basis a combination of muscimol and MK 801, an NMDA receptor antagonist, was investigated and shown to be effective (Lyden, P.D., Lonzo, L., *Stroke* **1994**, *25*, 189-196).

WO-A-99/25353 discloses the use of triazolo[4,3-b]pyridazine derivatives as benzodiazepine/$GABA_A$ modulators for the treatment of psychotic disorders and neurodegeneration.

WO-A-90/09174 discloses the use of the GABAergic agent Clomethiazole (chlormethiazole) in the prevention and/or treatment of neurodegeneration. Clomethiazole is thought to act through a GABAergic pathway, whereby it augments GABA's inhibitory effect on the CNS, giving the drug both hypnotic and neuroprotectant properties.

The clinical neuroprotectant profile of clomethiazole has been reviewed (Muckle, H., *IDrugs* **1999**, *2*, 184-193). A large-scale phase III trial has been completed in which clomethiazole was evaluated for its ability to reduce nerve damage in acute cerebrovascular ischaemia. A subgroup of patients who presented with large stroke, experienced a significant benefit. Of these (n = 545), 41% of treated patients were functionally independent after 90 days, compared to 30% of patients on placebo.

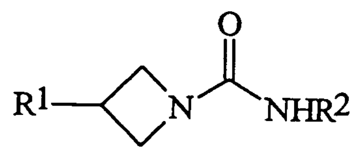
The effectiveness of this GABA modulator in rat (Snape, M.F., Baldwin, H.A., Cross, A.J., Green, A.R., *Neuroscience* **1993**, *53*, 837-844) and gerbil ischaemia (Cross, A.J., Jones, J.A., Baldwin, H.A., Green, A.R., *Br. J. Pharmacol.* **1991**, *104*, 406-411) has been demonstrated. The dose in the latter paradigm was 100 mg/kg, i.p.

Azetidine-1-carboxamides and the use of these compounds in the treatment of anxiety and all forms of epilepsy is described in International Patent Application No. PCT/GB99/00223.

There remains a medical need for new treatments for stroke and cerebrovascular disorders. The object of the present invention is to provide such treatments.

It has now been found that certain azetidine-1-carboxamides show unexpected neuroprotectant efficacy when compared to reference GABAergic agents. In particular, certain azetidine-1-carboxamides have been shown to potentiate the action of GABA in inhibiting neurones, and have also been shown to prevent the repetitive firing induced as a consequence of activation of glutamatergic mechanisms. Such compounds are found to be neuroprotective following acute cerebral ischaemia in rats and mice, and reduced ischaemia-induced CNS damage in *in vivo* models of focal ischaemia in both species.

According to the present invention, there is provided the use of a compound of formula (I)



(I)

wherein:

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

Reference in the present specification to an "alkyl" group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic or acyclic the alkyl group is preferably C_1 to C_{12}, more preferably C_1 to C_8 (such as methyl, ethyl, propyl, isopropyl butyl, isobutyl, tert-butyl, amyl, isoamyl, hexyl, heptyl, octyl).

Reference in the present specification to an "aryl" group means a mono or bicyclic aromatic group, such as phenyl or naphthyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 or 2 substituents. Substituents may include:

carbon containing groups such as

alkyl		
aryl,	arylalkyl	(e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen containing groups such as

haloalkyl	(e.g. trifluoromethyl);

oxygen containing groups such as

alcohols	(e.g. hydroxy, hydroxyalkyl, (aryl)(hydroxy)alkyl),
ethers	(e.g. alkoxy, alkoxyalkyl, aryloxyalkyl),
aldehydes	(e.g. carboxaldehyde),
ketones	(e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
acids	(e.g. carboxy, carboxyalkyl),
acid derivatives such as esters	(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkycarbonylyoxy, alkycarbonylyoxyalkyl) and amides (e.g. aminocarbonyl, mono- or dialkylaminocarbonyl, aminocarbonylalkyl, mono- or dialkylaminocarbonylalkyl, arylaminocarbonyl);

nitrogen containing groups such as

amines	(e.g. amino, mono- or dialkylamino, aminoalkyl, mono- or diälkylaminoalkyl),
azides,	
nitriles	(e.g. cyano, cyanoalkyl),
nitro;	

sulphur containing groups such as

thiols, thioethers, sulphoxides and sulphones	(e.g. alkylthio, alkylsulfinyl, alkylsufonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arylsulfinyl, arylsulfonyl, arylthioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and

heterocyclic groups containing one or more, preferably one, heteroatom,

(e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl,

pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl).

Preferred substituents include alkyl, aryl, halo, or an halogen-containing group such as trifluoromethyl.

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine or chlorine radical.

The compounds of formula (I) may exist in a number of diastereomeric and/or enantiomeric forms. Unless otherwise stated, reference in the present specification to "a compound of formula (I)" is a reference to all stereoisomeric forms of the compound and includes a reference to the unseparated stereoisomers in a mixture, racemic or non-racemic, and to each stereoisomer in its pure form.

In a preferred embodiment of the present invention, a compound of formula (I) is the (*R*)-enantiomer of the compound of formula (I), substantially free of its (*S*)-enantiomer.

In the compounds of formula (I), preferably R^1 is a substituted or unsubstituted aryl group selected from phenyl and naphthyl, more preferably R^1 is a substituted phenyl or naphthyl, more preferably R^1 is phenyl or naphthyl having 1 to 3 substituents and most preferably R^1 is phenyl or naphthyl having 1 or 2 substituents. In a preferred embodiment of the invention, R^1 is a mono- or di-substituted phenyl group, preferably a mono-substituted phenyl group.

Where R^1 is napthyl, it is preferred that R^1 is 2-naphthyl.

The preferred substituent groups are selected from halo (preferably fluoro and chlo trifluoromethyl and tertiary butyl, and more preferably from fluoro, chloro and trifluoromethyl.

Where R^1 is a phenyl having 1 substituent, the phenyl group is preferably para- or meta-substituted. Where R^1 is a phenyl having 2 substituents, the phenyl group is preferably 2,3-disubstituted, 2,4-disubstituted, 3,4-disubstituted or 3,5-disubstituted, preferably 3,4-disubstituted.

Where R^1 is disubstituted, it is preferred that R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group. More preferably, R^1 is dichloro-, difluoro-, chloro-fluoro- or fluoro-trifluoromethyl-substituted.

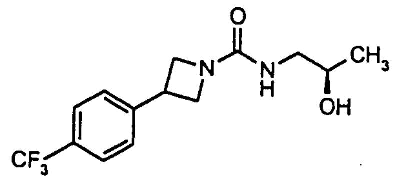
The R^1 groups are preferably selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

In one embodiment of the present invention R^2 is alkyl, preferably selected from C_{1-8} alkyl, more preferably from alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl and unsubstituted saturated cyclic and acyclic hydrocarbyl, and more preferably from propyl, 2-propenyl, 2-propynyl and 2-hydroxypropyl.

Particularly preferred compounds are as follows:-

Chirality	R^1	R^2
-	4-Cl-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propenyl
-	4-F-C_6H_4	2-propynyl
R	4-F-C_6H_4	$MeCH(OH)CH_2$
-	4-Cl-C_6H_4	2-propynyl
R	4-Cl-C_6H_4	$MeCH(OH)CH_2$
S	4-F-C_6H_4	$MeCH(OH)CH_2$
S	4-CF_3-C_6H_4	$MeCH(OH)CH_2$
-	3-CF_3-C_6H_4	2-propynyl
-	4-CF_3-C_6H_4	2-propynyl
R	4-CF_3-C_6H_4	$MeCH(OH)CH_2$
-	4-CF_3-C_6H_4	H

In a preferred embodiment of the present invention, the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ia)** or a pharmaceutically acceptable salt or prodrug thereof. In a particularly preferred embodiment of the present invention, the compound of formula (I) is the (*R*)-enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ib)**, substantially free of its (*S*)-enantiomer, or a pharmaceutically acceptable salt or prodrug thereof.



Compound Ib

According to a further aspect of the present invention there is provided a method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the present invention there is provided a method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising administration to a subject in need of such treatment an effective dose of the compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

The present invention may be employed in respect of a human or animal subject, more preferably a mammal, more preferably a human subject.

As used herein, the term "treatment" as used herein includes prophylactic treatment.

As used herein, the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I). For example, the compound of formula (I) may be prepared in a prodrug form wherein a free –OH group is derivatised (for example, via an ester, amide or phosphate bond) with a suitable group (the group may contain, for example, an alkyl, aryl, phosphate, sugar, amine, glycol, sulfonate or acid function) which is suitably labile so as it will be removed / cleaved (eg. by hydrolysis) to reveal the compound of formula (I) sometime after administration or when exposed to the desired biological environment.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic,

lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are hydrochloric, hydrobromic, phosphoric, sulfuric and methanesulfonic acids, and most particularly preferred is the methanesulfonate salt. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

As used herein, the term "substantially free of its (*S*)-enantiomer" means that the medicament or therapeutic composition comprising the compound of formula (I) used according to the present invention contains a greater proportion of the (*R*)-enantiomer of the compound of formula (I) in relation to the (*S*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention the term "substantially free of its (*S*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*R*)-enantiomer and 10 % by weight or less of the (*S*)-enantiomer. In a further preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains at least 99 % by weight of the (*R*)-enantiomer and 1 % or less of the (*S*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*S*)-enantiomer" means that the composition contains 100 % by weight of the (*R*)-enantiomer. The above percentages are based on the total amount of compound of formula (I) present in the medicament or therapeutic composition used according to the present invention.

The diseases, disorders and medical treatments/procedures to which the present invention is directed are:

Cerebral Ischaemia,

including transient ischaemic attack, stroke (thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke, lacunar stroke), subarachnoid haemorrhage, cerebral vasospasm, neuroprotection for stroke, peri-natal asphyxia, drowning, carbon monoxide poisoning, cardiac arrest and subdural haematoma;

Central Nervous System Injury,

including traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injury, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury; and

Eye Diseases,

including drug-induced optic neuritis, cataract, diabetic neuropathy, ischaemic retinopathy, retinal haemorrhage, retinitis pigmentosa, acute glaucoma, chronic glaucoma, macular degeneration, retinal artery occlusion and retinitis.

Additionally, the compound of formula (I) may also be used to potentiate the effects of other treatments, for example to potentiate the neuroprotective effects of brain derived nerve growth factor.

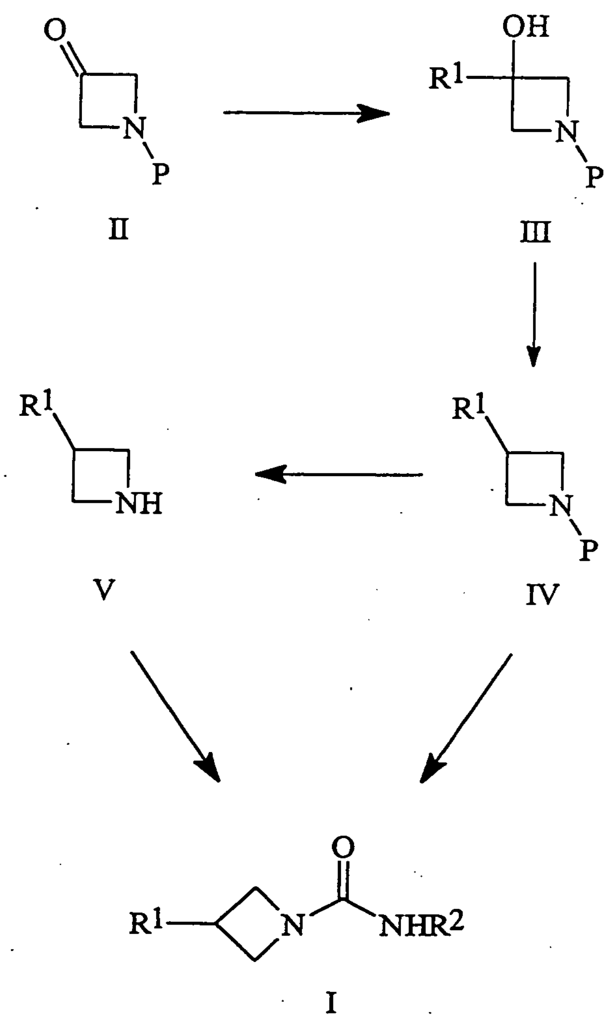
The invention is particularly directed to the treatment of cerebral ischaemia and central nervous system injury. The invention is also particularly directed to the treatment of post-asphyxial brain damage in new-born subjects.

The compound of formula (I) may be used in combination with one or more additional drugs useful in the treatment of the disorders mentioned above, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

Compounds of formula (I) may be prepared according to the reaction scheme (where P is a nitrogen protecting group). R^1 and R^2 are as previously defined. The 3-aryl-3-azetidinol (III) may be formed by treatment of the ketone (II) with an organometallic reagent such as an aryllithium or an arylmagnesium halide. Removal of the hydroxyl group to give the 3-arylazetidine (IV) may be effected by several methods including, for example, catalytic hydrogenolysis; treatment with lithium or sodium and ammonia; conversion to the xanthate by treatment with carbon disulphide, methyl iodide and base, followed by tin-mediated reduction; and conversion to the 3-aryl-3-chloroazetidine analogue using an alkylsulfonyl chloride and a base, followed by a reductive dechlorination using sodium, lithium or nickel. Formation of the azetidine (V) is achieved by reaction of (IV) with a suitable nitrogen deprotection agent. For example, if P is a diphenylmethyl group, then deprotection may be carried out by either catalytic transfer hydrogenation (e.g. ammonium formate and palladium catalyst) or by treatment with 1-chloroethyl chloroformate followed by methanol. The urea (I) is formed by reaction of azetidine (V) with an N-alkylisocyanate or an N-alkylcarbamoyl chloride and a base such as triethylamine or potassium carbonate. Alternatively, the urea may

be prepared directly from the azetidine (IV) without isolation of an intermediate such as the secondary amine (V). For example, when P is a diphenylmethyl group, azetidine (IV) may be treated with phosgene followed by amine R^2NH_2 to give urea (I) directly.

Reaction Scheme



The invention further provides a pharmaceutical composition comprising an effective amount of the compound of formula (I) in combination with a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining an effective amount of the compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

To further increase efficacy, the composition may contain components such as dextran or cyclodextrins or ether derivatives thereof, which aid stability and dispersion, and decrease metabolism of the active ingredient.

For compositions in which the pharmaceutically acceptable carrier comprises a cyclodextrin or an ether derivative thereof, the active ingredient is intimately mixed with an aqueous solution of the cyclodextrin or ether derivative thereof, with optional addition of further pharmaceutically acceptable ingredients before, during or after said mixing. The thus obtained solution is optionally lyophilized, and the lyophilized residue is optionally reconstituted with water.

In an embodiment of the present invention, the composition further comprises a buffer system, an isotonizing agent and water.

Compounds of formula (I) may be administered in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use including transmucosal and transdermal use, for example a cream, ointment, gel, aqueous or oil solution or suspension, salve, patch or plaster; for nasal use, for a example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example a finely divided powder or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oil solution or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients, using standard techniques well known to those skilled in the art of pharmacy. Preferably, the compound is administered orally.

For oral administration, the compounds of formula (I) will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose,

while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of formula (I) will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

It will be appreciated that the dosage levels used may vary over quite a wide range depending upon the compound used, the severity of the symptoms exhibited by the patient and the patient's body weight.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the examples are intended to illustrate and not to limit the scope of the present invention.

EXAMPLES

Synthetic Examples

1-(Diphenylmethyl)-3-azetidinol (2)

The compound (2) was prepared according to the method of Anderson and Lok (*J. Org. Chem.* **1972**, *37*, 3953, the disclosure of which is incorporated herein by reference), m.p. 111-112 °C (lit. m.p. 113 °C).

1-Diphenylmethyl-3-azetidinone (3)

Dimethyl sulfoxide (0.36 mL, 5 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.40 mL, 4.6 mmol) in dichloromethane (20 mL) at -78 °C under an argon atmosphere. The mixture was stirred for 10 minutes then a solution of 1-(diphenylmethyl)-3-azetidinol (1.0 g, 4.2 mmol) in dichloromethane (20 mL) was added dropwise. The mixture was warmed to -50 °C and stirred for 30 minutes. Triethylamine (2.9 mL, 21 mmol) was added and the mixture warmed to room temperature. After 1 hour, water (50 mL) was added and the mixture extracted with dichloromethane (4 x 50 mL). The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated *in vacuo* to give 1-diphenylmethyl-3-azetidinone (3) as a pale yellow crystalline solid (1.0 g, 99 %) (lit. (S.S. Chatterjee and A. Shoeb, *Synthesis*, 1973,153) m.p. 82°C).

3-(4-Chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4)

To a stirred solution of 4-chlorophenylmagnesium bromide (9.1 mL, 1.0M in diethyl ether) in diethyl ether (80 mL) at -78 °C under an argon atmosphere was added compound 3 (1.8 g, 7.6 mmol) in diethyl ether (50 mL) dropwise over 20 minutes. The reaction mixture was stirred at -78 °C for 2 hours, then slowly warmed to room temperature with stirring over 18 hours. The reaction mixture was then partitioned between aqueous ammonium acetate solution (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were washed (water, brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product as a pale yellow viscous oil in quantitative yield. A sample purified for analysis by column chromatography on silica gel using 15-30% ethyl acetate-hexane as eluent and subsequent crystallisation from hexane gave 3-(4-

chlorophenyl)-1-(diphenylmethyl)-3-azetidinol (4), m.p. 108°C. Found: C, 75.42; H, 5.79; N, 3.98. $C_{22}H_{20}ClNO$ requires C, 75.53; H, 5.76; N, 4.00%.

O-(3-(3-(4-Chlorophenyl)-1-diphenylmethyl))azetidinyl)-S-methyldithiocarbonate (5)

To a stirred suspension of sodium hydride (0.4 g of a 60% suspension in mineral oil, 10.4 mmol) (prewashed with hexane) in THF (80 mL) was added dropwise a solution of compound 4 (1.7 g, 4.9 mmol) in THF (80 mL). The mixture was stirred for 3 hours then carbon disulphide (17.6 mL, 0.29 mol) and methyl iodide (6.1 mL, 0.1 mol) were added dropwise. The mixture was stirred at room temperature for 15 hours and then heated to 50 °C while the solvent was removed in a stream of argon. When the volume of the mixture was reduced by half, the mixture was concentrated *in vacuo* to an approximate volume of 20 mL and then partitioned between water and diethyl ether. The organic layer was washed with water and then brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was crystallised from hexane to give *O*-(3-(3-(4-chlorophenyl)-1-diphenylmethyl))azetidinyl)-*S*-methyldithiocarbonate (5) (2.06g, 96%).

3-(4-Chlorophenyl)-1-(diphenylmethyl)azetidine (6)

To a stirred solution of tributyltin hydride (1.8 mL, 6.9 mmol) in dry toluene (40 mL) at reflux under an argon atmosphere was added dropwise, over 1 hour, a solution of compound 5 (2.0 g, 4.6 mmol) in toluene (40 mL). The mixture was heated under reflux for a further 2 hours then was concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica gel using hexane and then 10% ethyl acetate-hexane as eluent. The product was recrystallised twice from hexane to give 3-(4-chlorophenyl)-1-(diphenylmethyl)azetidine (6) (0.4 g, 34%) m.p. 82 °C. Found: C, 78.94; H, 6.06; N, 4.14. $C_{22}H_{20}ClN$ requires C, 79.15; H, 6.04; N, 4.20%.

3-(4-Chlorophenyl)azetidine (7)

To a solution of compound 6 (0.36 g, 1.1 mmol) in 1,2-dichloroethane (10 mL) containing proton sponge (0.02 g), cooled in an ice-water bath under an argon atmosphere, was added

dropwise 1-chloroethyl chloroformate (0.3 mL, 3.1 mmol). The resultant solution was bc at reflux for 4 hours, cooled and was concentrated *in vacuo*. The residue obtained was mixed with methanol (10 mL) and heated under reflux for 2 hours, then cooled and concentrated *in vacuo* to give the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) which was used without further purification.

Example 1. 3-(4-Chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8)

To the hydrochloride salt of 3-(4-chlorophenyl)azetidine (7) (approximately 1.1 mmol) in ethanol (10 mL) stirred at 0°C was added sequentially and dropwise allyl isocyanate (0.15 mL, 1.7 mmol) followed by triethylamine (0.3 mL, 2.2 mmol). After 20 minutes the reaction mixture was partitioned between aqueous ammonium chloride and ether. The organic layer was washed (water and then brine), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a crude product. The product obtained was purified by column chromatography on silica gel using 20% ethyl acetate-hexane as eluent to give 3-(4-chlorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (8) which was recrystallised from cyclohexane/toluene (0.16 g, 61%), m.p. 112 °C. Found: C, 62.20; H, 6.23; N, 11.40. $C_{13}H_{15}ClN_2O$ requires C, 62.28; H, 6.03; N, 11.17%.

3-(4-tert-Butylphenyl)-1-diphenylmethyl-3-azetidinol (9)

To a stirred solution of 4-tert-butylphenylmagnesium bromide (11.5 mL, 2.0M (Et_2O)) in toluene (50 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-azetidinone (3) (5.0 g) in toluene (100 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 50 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from cyclohexane gave 3-(4-tert-butylphenyl)-1-diphenylmethyl-3-azetidinol (9) (6.23 g), m.p. 168-169°C (cyclohexane). Found: C. 83.68; H, 7.97; N, 3.72. $C_{26}H_{29}NO$ requires C, 84.06; H, 7.87; N, 3.77%.

3-(4-tert-Butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10)

To a stirred solution of compound (9) (6.23 g) and N,N-diisopropylethylamine (3.5 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.4 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) m.p. 145°C (hexane). Found: C, 80.30; H, 7.05; N, 3.64. $C_{26}H_{28}ClN$ requires C, 80.08; H, 7.24; N, 3.59%.

3-(4-tert-Butylphenyl)-1-(diphenylmethyl)azetidine (11)

To a stirred suspension of Raney Nickel (8.6 g, wet slurry) in tertiary butanol (50 mL) and toluene (50 mL) was added a solution of 3-(4-tert-butylphenyl)-3-chloro-1-(diphenylmethyl)azetidine (10) (4.73 g) in toluene (10 mL). The mixture was heated to 80°C for 6 hours, cooled to room temperature and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 50 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (10% ethyl acetate/hexane) on silica. Recrystallisation from methanol gave 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (3.40 g), m.p. 95°C (methanol). Found: C, 87.84; H, 8.17; N, 3.92. $C_{26}H_{29}N$ requires C, 87.84; H, 8.22; N, 3.94%.

Example 2. 3-(4-tert-Butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (1.0 g) in dichloromethane (10 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (10 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.8 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (30 mL), washed (water, brine), dried (Na_2SO_4), concentrated in vacuo and purified by flash column chromatography (50% ethyl acetate-hexane) to give 3-(4-tert-butylphenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (12) (0.21 g), m.p. 98-99°C (diisopropyl ether). Found: C, 74.95; H, 8.97; N, 10.25. $C_{17}H_{24}N_2O$ requires C, 74.96; H, 8.88; N, 10.28%.

Example 3. 3-(4-tert-Butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.5 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring propargylamine (0.24 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Trituration with diethyl ether (2 mL) gave 3-(4-tert-butylphenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (13) (0.14 g), m.p. 141°C (diethyl ether). Found: C, 75.40; H, 8.19; N, 10.38. $C_{17}H_{22}N_2O$ requires C, 75.52; H, 8.20; N, 10.36%.

Example 4. (R)-3-(4-tert-Butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14)

To a stirred solution of 3-(4-tert-butylphenyl)-1-(diphenylmethyl)azetidine (11) (0.50 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (0.8 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.25 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) concentrated in vacuo and purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-tert-butylphenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (14) (0.35 g), m.p. 96-97°C (diisopropyl ether). Found: C, 69.59; H, 8.74; N, 9.23. $C_{17}H_{26}N_2O$ requires C, 70.31; H, 9.02; N, 9.64%.

3-(4-Fluorophenyl)-1-diphenylmethyl-3-azetidinol (15)

To a stirred solution of 4-fluorophenylmagnesium bromide (7.0 mL, 1.0M (Et_2O)) in toluene (20 mL) at -78°C under argon, was added, dropwise, a solution of 1-diphenylmethyl-3-

azetidinone (3) (1.4 g) in toluene (30 mL) over 30 minutes. The mixture was stirred for 4 hours at -78°C then warmed to room temperature and partitioned between aqueous ammonium chloride solution (50 mL) and diethyl ether (3 x 20 mL). The combined organic fractions were washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (20% ethyl acetate, hexane) gave 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (1.82 g). To a stirred solution of the free base (1.82 g) in ether (5 mL) was added dropwise a solution of oxalic acid (0.49 g) in acetone (1 mL). The mixture was stirred for 5 minutes then filtered to give the oxalate salt hemihydrate (2.23 g), m.p. 75°C (acetone). Found: C, 66.71; H, 5.34; N, 3.04. $C_{24}H_{22}FNO_5.0.5H_2O$ requires C, 66.67; H, 5.32; N, 3.17%.

3-(4-Fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16)

To a stirred solution of 3-(4-fluorophenyl)-1-diphenylmethyl-3-azetidinol (15) (4.0 g) and N,N-diisopropylethylamine (3.2 mL) in dichloromethane (100 mL) at 0°C was added, dropwise, methanesulfonyl chloride (1.25 mL). The mixture was stirred at 0°C for 18 hrs, then washed (water, brine) and dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallised from hexane to give 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (2.2 g), m.p. 108-109°C (hexane). Found: C, 75.13; H, 5.46; N, 3.93. $C_{22}H_{19}ClFN$ requires C, 75.10; H, 5.44; N, 3.98%.

3-(4-Fluorophenyl)-1-(diphenylmethyl)azetidine (17)

To a stirred suspension of Raney Nickel (2.0 g, wet slurry) in tertiary butanol (10 mL) and toluene (50 mL) was added a solution of 3-(4-fluorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (16) (1.9 g) in toluene (20 mL). The mixture was heated to 80°C for 6 hours, cooled and filtered through kieselguhr. The filtrate was concentrated in vacuo and partitioned between diethyl ether (3 x 30 mL) and aqueous potassium carbonate solution (50 mL). The combined organic extracts were washed (water, brine), dried (Na_2SO_4), and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (1.5 g), m.p. 65-66°C (diisopropyl ether). Found: C, 83.25; H, 6.35; N, 4.41. $C_{22}H_{20}FN$ requires C, 83.25; H, 6.35; N, 4.41%.

Example 5. 3-(4-Fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18)

To a stirred solution of 3-(4-fluorophenyl)-*N*-(diphenylmethyl)azetidine (17) (0.67 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (2.5 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring, allylamine (0.5 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from diisopropyl ether gave 3-(4-fluorophenyl)-*N*-(2-propenyl)azetidine-1-carboxamide (18) (0.30g), m.p. 119-120°C (diisopropyl ether). Found: C, 66.61; H, 6.37; N, 11.74. $C_{13}H_{15}FN_2O$ requires C, 66.65; H, 6.45; N, 11.95%.

Example 6. 3-(4-Fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.38 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.4 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added, dropwise, with stirring propargylamine (0.3 mL). The mixture was stirred for 18 hrs at room temperature, diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash column chromatography (50% ethyl acetate hexane) and then crystallised from diisopropyl ether to give 3-(4-fluorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (19) (0.14g), m.p. 141°C (diisopropyl ether). Found: C, 67.32; H, 5.65; N, 11.93. $C_{13}H_{13}FN_2O$ requires C, 67.23; H, 5.64; N, 12.06%.

Example 7. (R)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20)

To a stirred solution of 3-(4-fluorophenyl)-1-(diphenylmethyl)azetidine (17) (0.35 g) in dichloromethane (5 mL) at 0°C was added dropwise a solution of 20% phosgene in toluene (1.2 mL). The mixture was stirred for 90 minutes then concentrated in vacuo. To the concentrate was added dichloromethane (5 mL) and to this solution at 0°C was added dropwise with stirring (R)-1-amino-2-propanol (0.2 mL). The mixture was stirred for 18 hrs

at room temperature,diluted with dichloromethane (20 mL), washed (water, brine), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash column chromatography (10% methanol-ethyl acetate) to give (R)-3-(4-fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (20) (0.21g), m.p. 104-105 °C (toluene/ethanol). Found: C, 61.93; H, 6.97; N, 10.9. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

Example 8. (3-(4-Chlorophenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (21)

This compound was prepared from 3-(4-chlorophenyl-1-(diphenylmethyl)azetidine (6) and propargylamine using the procedure outlined in Example 3, m.p. 160 °C (diethyl ether). Found C, 62.85; H, 5.38; N, 10.89 $C_{13}H_{13}ClN_2O$ requires C, 62.78; H, 5.27; N, 11.26%.

Example 9. (R)-3-(4-Chlorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (22)

This compound was prepared from compound (6) and (R)-1-amino-2-propanol using the procedure outlined in Example 4, m.p. 92-93 °C (diethyl ether-toluene). Found: C, 58.97; H, 6.38; N, 9.96. $C_{13}H_{17}ClN_2O_2.0.2PhCH_3$, requires C, 60.23; H, 6.48; N, 9.76%.

Example 10: (*S*)-3-(4-Fluorophenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide (23)

This compound was prepared from compound (17) and (*S*)-1-amino-2-propanol using the procedure described for compound (20). m.p. 102-104°C. Found: C, 61.94; H, 6.72; N, 11.1. $C_{13}H_{17}FN_2O_2$ requires C, 61.89; H, 6.79; N, 11.10%.

3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidin-3-ol (24)

This compound was prepared from compound (3) and 3,4-dichlorophenylmagnesium bromide using the procedure described for compound (4).

3-(3,4-Dichlorophenyl)-3-chloro-1-(diphenylmethyl)azetidine (25)

This compound was prepared from compound (24) using the procedure described compound (10).

3-(3,4-Dichlorophenyl)-1-(diphenylmethyl)azetidine (26)

This compound was prepared from compound (25) using the procedure described from compound (11).

Example 11. 3-(3,4-Dichlorophenyl)-*N*-(2-propynyl)azetidine carboxamide (27)

This compound was prepared from compound (26) and propargylamine using the procedure described for compound (12). m.p. 105.5-107.5°C.

Example 12. (R)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (28)

This compound was prepared from compound (26) and (*R*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.58; H, 5.33; N, 9.26. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

Example 13. (S)-3-(3,4-Dichlorophenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (29)

This compound was prepared from compound (26) and (*S*)-1-amino-2-propanol using the procedure described for compound (12). m.p. 123-125°C. Found: C, 51.47; H, 5.30; N, 9.18. $C_{13}H_{16}Cl_2N_2O_2$ requires C, 51.50; H, 5.32; N, 9.24%.

3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (30)

This compound was prepared from compound (3) and 4-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(4-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (31)

This compound was prepared from compound (30) using the procedure described for compound (10).

3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32)

This compound was prepared from compound (31) using the procedure described for compound (11).

Example 14. (R)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (33)

This compound was prepared from compound (32) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.78; H, 5.75; N, 9.01. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71, N, 9.13%.

Example 15. (S)-3-(4-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (34)

This compound was prepared from compound (32) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 107-108°C. Found: C, 54.75; H, 5.68; N, 9.09. $C_{14}H_{17}F_3N_2O_2.0.25\ H_2O$ requires C, 54.81; H, 5.71; N, 9.13%.

Example 16. 3-(4-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (35)

This product was prepared from compound (32) and propargylamine using the procedure described for compound (12). m.p. 151-155°C.

3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidin-3-ol (36)

This compound was prepared from compound (3) and 3-(trifluoromethyl)phenylmagnesium bromide using the procedure described for compound (4).

3-Chloro-3-(3-(trifluoromethyl)phenyl)-(diphenylmethyl)azetidine (37)

This compound was prepared from compound (32) using the procedure described for compound (10).

3-(3-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (38)

This compound was prepared compound (37) using the procedure described for compo (11).

Example 17. (R)-3-(3-(Trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine carboxamide (39)

This compound was prepared from compound (38) and (R)-1-amino-2-propanol using the procedure described for compound (12). m.p. 81-82°C.

Example 18. (S)-3-(3-(Trifluoromethyl)phenyl)-*N*-(-2-hydroxypropyl)azetidine carboxamide (40)

This compound was prepared from compound (38) and (S)-1-amino-2-propanol using the procedure described for compound (12). m.p. 80-82°C.

Example 19. 3-(3-(Trifluoromethyl)phenyl)-*N*-(2-propynyl)azetidine-1-carboxamide (41)

This product was prepared from compound (38) and propargylamine using the procedure described for compound (12). m.p. 121°C.

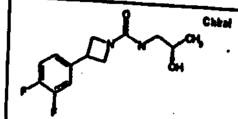
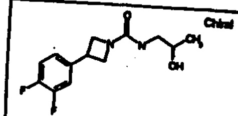
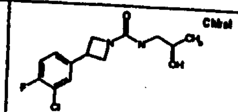
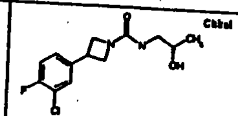
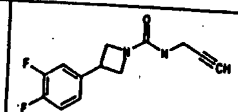
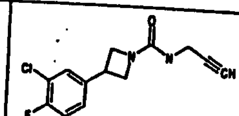
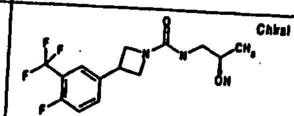
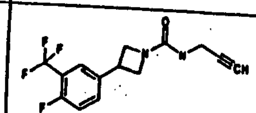
Example 20. 3-(4-(Trifluoromethyl)phenyl)-N-azetidine-1-carboxamide (42)

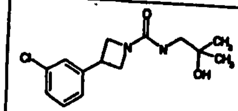
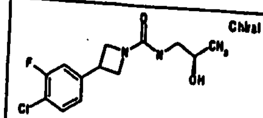
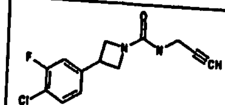
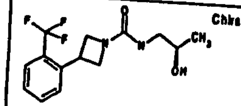
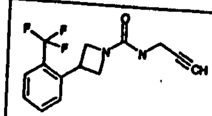
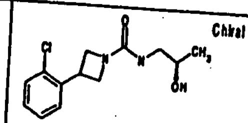
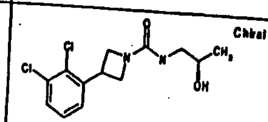
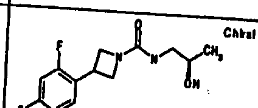
To a solution of 3-(4-(Trifluoromethyl)phenyl)-1-(diphenylmethyl)azetidine (32) (8.2 mmol) in dichloromethane (20 mL) at 0°C, was added a solution of phosgene (1.75M in toluene, 10.2 mmol). The reaction mixture was stirred at room temperature for 90 minutes, concentrated *in vacuo*, then redissolved in THF (25 mL), cooled to 0°C and treated with ammonium hydroxide (12.5 mL). The reaction was stirred for 16 h, then water (80 mL) and ethyl acetate (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL), combined organic layers washed with brine (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated using ethyl acetate (60 mL) to a solid (1.64 g, 81%), mp. 207.5-208.5-°C (ethyl acetate). Found: C, 54.51; H, 4.59; N, 11.41. $C_{14}H_{17}ClN_2O_2$ requires: C, 54.10; H, 4.54; N, 11.47.

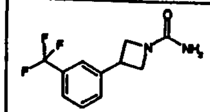
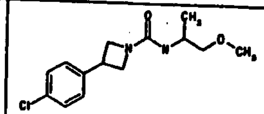
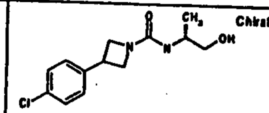
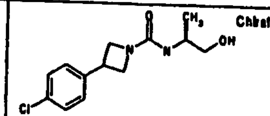
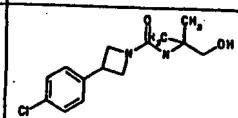
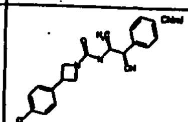
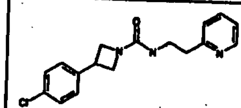
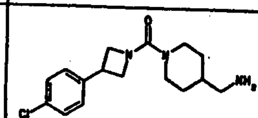
Examples 21 to 84 – See Table 1

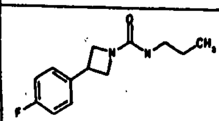
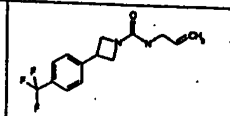
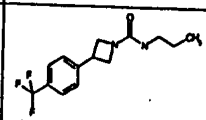
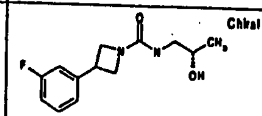
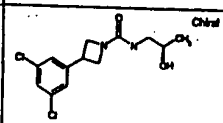
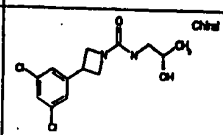
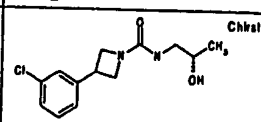
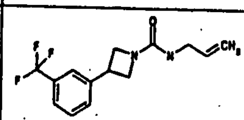
These products were prepared using the procedure described for compound 12.

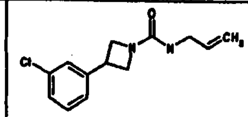
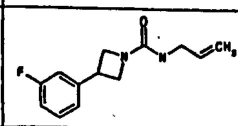
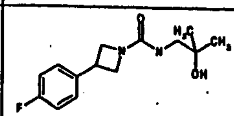
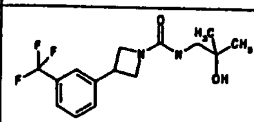
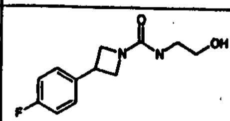
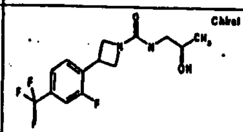
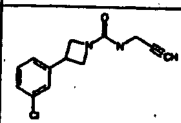
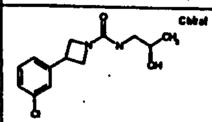
Table 1

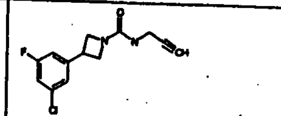
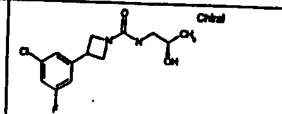
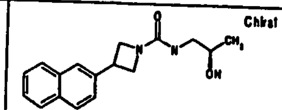
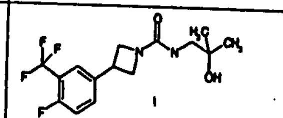
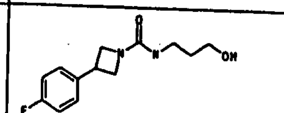
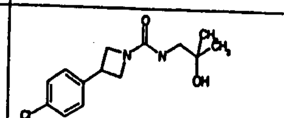
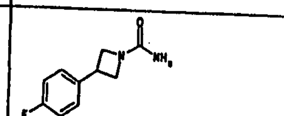
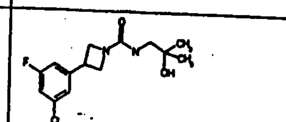
Example No.	C mpound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
21	43		$C_{13}H_{16}F_2N_2O_2$	270.28	108-109	57.79	5.96	10.28	57.77	5.97	10.36	
22	44		$C_{13}H_{16}F_2N_2O_2$	270.28	108-109	57.73	5.95	10.29	57.77	5.97	10.36	
23	45		$C_{13}H_{16}ClFN_2O_2$	286.74	83-84	54.44	5.65	9.74	54.46	5.62	9.77	
24	46		$C_{13}H_{16}ClFN_2O_2$	286.74	83-84	54.46	5.69	9.63	54.46	5.62	9.77	
25	47		$C_{13}H_{12}F_2N_2O$	250.25	123.0	62.36	4.81	11.20	62.40	4.83	11.19	
26	48		$C_{13}H_{12}ClFN_2O$	266.70	133.0	58.56	4.53	10.45	58.55	4.53	10.50	
27	49		$C_{14}H_{16}F_4N_2O_2$	320.29	69-71	52.44	5.02	8.69	52.50	5.03	8.74	
28	50		$C_{14}H_{12}F_4N_2O$	300.26	119.0	56.05	4.02	9.26	56.00	4.03	9.33	

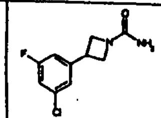
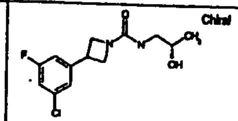
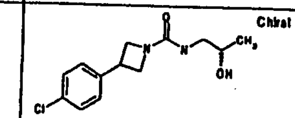
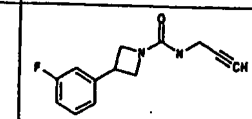
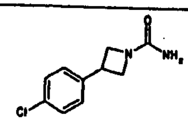
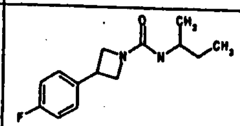
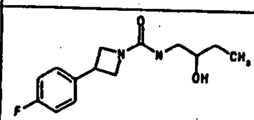
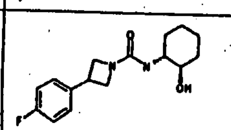
Example N .	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
29	51		C14H19ClN2O2	282.77	102.0	59.69	6.69	9.80	59.47	6.77	9.90	
30	52		C13H16ClFN2O2	286.74	oil							
31	53		C13H12ClFN2O	266.70	132.0	58.53	4.58	10.45	58.55	4.53	10.50	a
32	54		C14H17F3N2O2	302.30	89.0	55.65	5.64	9.20	55.63	5.67	9.26	
33	55		C14H13F3N2O	282.27	101.0	59.70	4.55	9.96	59.57	4.64	9.92	
34	56		C13H17ClN2O2	268.75	109.0	57.15	6.35	10.28	58.10	6.38	10.42	
35	57		C13H16Cl2N2O2	303.19	111.0	51.43	5.24	9.19	51.50	5.32	9.24	
36	58		C13H16F2N2O2	270.28	88-89	57.74	6.11	10.34	57.77	5.97	10.36	

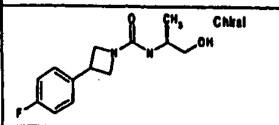
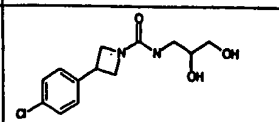
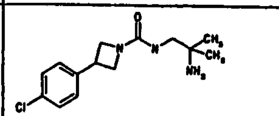
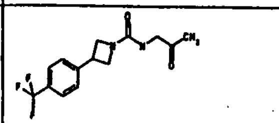
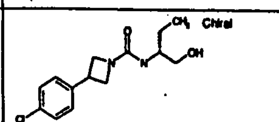
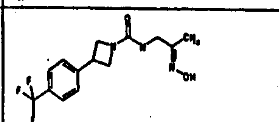
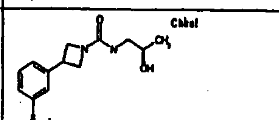
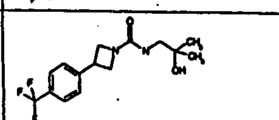
Example N .	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
37	59		C11H11F3N2O	244.22	198.0	54.14	4.55	11.47	54.10	4.54	11.47	
38	60		C14H19ClN2O2	282.77	110.0	59.33	6.79	9.95	59.47	6.77	9.90	
39	61		C13H17ClN2O2	268.75	71-75							b
40	62		C13H17ClN2O2	268.75	82-85	58.09	6.41	10.36	58.10	6.38	10.42	
41	63		C14H19ClN2O2	282.77	134-135	59.31	6.86	10.02	59.47	6.77	9.90	
42	64		C19H21ClN2O2	344.84	120-122							c
43	65		C17H18ClN3O	315.81	125.0	64.75	5.74	13.27	64.66	5.74	13.30	
44	66		C16H22ClN3O	307.83	137-138	49.82	6.33	10.13	50.55	6.49	10.40	

Example N.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
45	67		C13H17FN2O	236.29	117-118.5	66.12	7.18	11.83	66.08	7.25	11.86	
46	68		C14H15F3N2O	284.28	136-137.5	59.26	5.39	9.93	59.15	5.32	9.85	
47	69		C14H17F3N2O	286.30	127-128.5	58.69	5.89	10.03	58.73	5.98	9.78	
48	70		C13H17FN2O2	252.29	79.5-80	61.91	6.77	11.09	61.89	6.79	11.10	
49	71		C13H16Cl2N2O2	303.19	110-111	51.67	5.35	9.21	51.50	5.32	9.24	
50	72		C13H16Cl2N2O2	303.19	110-111	52.00	5.41	9.24	51.50	5.32	9.24	
51	73		C13H17ClN2O2	268.75	78-80	58.44	6.13	10.39	58.10	6.38	10.42	
52	74		C14H15F3N2O	284.28	64-66	58.94	5.32	10.15	59.15	5.32	9.85	

Example N .	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Note
53	75		C13H15ClN2O	250.73	65-66	62.75	5.97	11.09	62.28	6.03	11.17	
54	76		C13H15FN2O	234.28	62.5-63.5	66.52	6.52	11.90	66.65	6.45	11.95	
55	77		C14H19FN2O2	266.32	77-78.5	63.25	7.25	10.52	63.14	7.19	10.51	
56	78		C15H19F3N2O2	316.33	94.5-96	57.00	5.85	8.82	56.96	6.05	8.85	
57	79		C12H15FN2O2	238.26	99-101	60.41	6.35	11.72	60.49	6.35	11.75	
58	80		C14H16F4N2O2	320.29	106-107	52.41	5.11	8.71	52.50	5.03	8.74	
59	81		C13H13ClN2O	248.71	90-105 decom.	62.67	5.27	11.10	62.78	5.27	11.26	
60	82		C13H17ClN2O2	268.75	75-76.5	58.18	6.38	10.32	58.10	6.38	10.42	

Example N.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
61	83		C13H12ClFN2O	266.70	108.5-110	58.50	4.44	10.53	58.55	4.53	10.50	
62	84		C13H16ClFN2O2	286.74	79-80.5	54.61	5.77	9.69	54.46	5.62	9.77	
63	85		C17H20N2O2	284.36	143-144	71.63	7.11	9.78	71.81	7.09	9.85	
64	86		C15H18F4N2O2	334.32	110-111.5	53.85	5.51	8.34	53.89	5.42	8.38	
65	87		C13H17FN2O2	252.29	90-93	62.09	6.70	10.78	61.89	6.79	11.10	
66	88		C14H19ClN2O2	282.77	114-115.5	59.52	6.88	9.62	59.47	6.77	9.91	
67	89		C10H11FN2O	194.21	205-208.5	61.74	5.70	14.21	61.85	5.71	14.42	
68	90		C14H18ClFN2O2	300.76	112.5-113.5	55.86	6.07	9.33	55.91	6.03	9.31	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
69	91		C10H10ClFN2O	228.66	198-200.5							
70	92		C13H16ClFN2O2	286.74	81-82.5							
71	93		C13H17ClN2O2	268.75	92.5-94	58.23	6.41	10.26	58.10	6.38	10.42	
72	94		C13H13FN2O	232.26	101.5-10.25	67.13	5.60	12.03	67.23	5.64	12.06	
73	95		C10H11ClN2O	210.66	oil							d
74	96		C14H19FN2O	250.32	100-102	67.10	7,64	11.05	67.18	7.65	11.19	
75	97		C14H19FN2O2 (0.3 H2O)	266.32	77-79	61.83	7.30	10.39	61.74	7.28	10.29	
76	98		C16H21FN2O2	292.36	141-142.5	65.71	7.31	9.52	65.73	7.24	9.58	

Example No.	Compound No.	Structure	Formula	MWt	mp	Cfound	Hfound	Nfound	Cexp	Hexp	Nexp	Not
77	99		C13H17FN2O2	252.29	118-120	61.59	6.89	10.95	61.89	6.79	11.10	
78	100		C13H17ClN2O3	284.75	90-92	54.93	6.07	9.79	54.84	6.02	9.83	
79	101		C14H20ClN3O.HCl	318.25	183-184	52.76	6.77	13.04	52.84	6.65	13.20	
80	102		C14H15F3N2O2	300.28	139.5-141	56.07	5.05	9.27	56.00	5.03	9.32	f
81	103		C14H19ClN2O2	282.77	oil							e
82	104		C14H16F3N3O2	315.30	>150 decom.	53.05	5.18	13.24	53.33	5.11	13.32	g
83	105		C13H17FN2O2	252.29	77.5-79	61.82	6.83	11.05	61.89	6.79	11.10	
84	106		C15H19F3N2O2	316.33	123-124	57.03	6.08	8.88	56.96	6.05	8.85	

Footnotes for Table 1:

Footnote a: IR: 3373, 3316, 2923, 2855, 1639, 1620, 1557, 1488, 1462, 1434, 1378, 1304, 1153, 815 cm^{-1}.

Footnote b: IR: 3500, 3429, 3346, 3274, 2925, 2854, 1614, 1556, 1466, 1420, 1407, 1052, 824, 536 cm^{-1}.

Footnote c: IR: 3414, 3320, 3253, 2925, 2855, 1606, 1544, 1492, 1460, 1376, 1316, 1092, 822, 751, 705 cm^{-1}.

Footnote d: IR: 3340, 3166, 2923, 2854, 1650, 1613, 1493, 1460, 1378, 1303, 1098, 820 cm^{-1}.

Footnote e: IR: 3310, 2964, 2878, 1632, 1538, 1494, 1482, 1462, 1398, 1328, 1093, 1015, 823, 529 cm^{-1}.

Footnote f: compound (102) was made by the oxidation of compound (33), by methods known to those skilled in the art.

Footnote g: compound (104) was made from compound (102) by methods known to those skilled in the art.

Testing Procedures

Rat transient middle cerebral artery occlusion (MCAo) ischaemia model

This model of middle cerebral artery occlusion used relies on an intraluminal filament technique in the rat (Zhao Q. *et al., Acta Physiol. Scand.* 1994, *152,* 349-350). Male Lister Hooded rats were used in these experiments and were divided into three groups (Group 1: vehicle; Group 2: chlomethiazole (CMZ); Group 3: compound (Ib)). The sample size in each was 11 to 15. The animal was anaesthetised and the carotid artery exposed. A chamfered monofilament suture (3/0) of a specified diameter was introduced into the ligated carotid artery, past the bifurcations of the external and common carotid, the internal carotid and the pterygopalatine artery, into the intracranial circulation. The filament then lodged in the narrow proximal anterior carotid occluding the middle cerebral artery. After 90 min. of middle cerebral artery occlusion, the filament was removed, allowing re-circulation.

22.5 h following reperfusion, the animal was perfused *via* the transaortic route, using 200 ml of a 3 percent solution of tetrazolium chloride warmed to 37° C. Following perfusion, the brain was removed and immersion fixed in 10 percent formalin/saline for at least 48 h. Following fixation, the brain was sliced into 0.5 mm sections on a vibroslice. Using this technique, viable tissue was stained dark red and infarcted tissue remains unstained. The area of infarction on each section was measured, and the total volume of infarction in the hemisphere, cortex and striatum computed, using the Kontron image analysis system.

The experimental data are displayed in Figure 1 which shows the effect of (i) vehicle; (ii) 128 mg/kg of clomethiazole dosed intraperitoneally (i.p.); and (iii) 30 mg/kg i.p. of compound (Ib), on infarct volumes (assessed using tetrazolium histochemistry) after transient middle cerebral artery occlusion. Data are displayed as (mean + SEM) using absolute infarct volumes in mm^3. In Figure 1, ** signifies $p < 0.01$, and * signifies $p < 0.05$ in the t test.

Figure 1 illustrates that compound (Ib) exhibits significant neuroprotection at a dose of 30 mg/kg i.p. in the rat transient MCAo model. Clomethiazole at a dose of 128 mg/kg i.p. was found not to be effective in this model (see Sydserff, S.G. *et al.,. Br. J. Pharmacol.* **1995,** *114,* 1631-1635).

Mouse permanent middle cerebral artery occlusion ischaemia model

Adult male C57Bl mice (20-25 g, n = 10 per group) were administered compound (Ib) (10 mg/kg) or vehicle (60% PEG400 in water) i.p. 30 minutes prior to middle cerebral artery (MCA) occlusion. Under halothane anaesthesia (1.5% halothane in nitrous oxide: oxygen (70:30)), a small craniectomy was made to expose the left MCA. The distal portion of the MCA was occluded by electrocoagulation. The incision site was sutured and anaesthetics withdrawn. 24 h following MCA occlusion, the mouse was euthanised, the brain removed and immersed in 4% triphenyltetrazolium chloride to visualise the area of infarction (Backhaus C. *et al., J. Pharm Methods* **1992,** *27,* 27-32). Brains were then stored in 10% formalin/saline. The area of infarction as visible on the cortical surface was then computed using a PC digital imaging system (KS300, Imaging Associates, UK). Data generated is

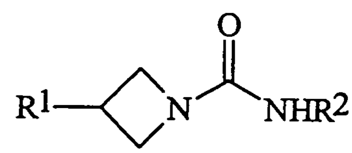
absolute area of infraction in mm^2 for each animal. Mean infarct areas were compared unpaired t-tests with significance taken at $p < 0.05$.

The experimental results are displayed in Figure 2 which shows the effect of (i) vehicle; and (ii) 60 mg/kg i.p. of compound (Ib) on infarction after permanent middle cerebral artery occlusion.

Figure 2 shows that that compound (Ib) exhibits significant neuroprotection at a dose of 60 mg/kg i.p. in the mouse permanent MCAo model.

CLAIMS

1. Use of a compound of formula (I)



(I)

wherein

R^1 is aryl; and

R^2 is hydrogen or alkyl;

or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for neuroprotection in a subject or for the treatment of cerebral ischaemia, central nervous system injury or eye diseases.

2. A use according to claim 1 wherein R^1 is an aryl group selected from phenyl and naphthyl.

3. A use acording to claim 1 or 2 wherein R^1 has 1, 2 or 3 substituent groups.

4. A use according to any preceding claim wherein R^1 is substituted with one or more substituent groups selected from halo, trifluoromethyl and tertiary-butyl.

5. A use according to claim 4 wherein said halo groups are selected from chloro and fluoro.

6. A use according to claim 1, 2, 3, 4 or 5 wherein R^1 is a meta- or para-substituted phenyl group.

7. A use according to claim 1 wherein R^1 is selected from 4-chlorophenyl, 4-fluorophenyl, 4-(trifluoromethyl)phenyl and 3-(trifluoromethyl)phenyl.

8. A use according to claim 1, 2, 3, 4 or 5 wherein R^1 is selected from a 2,3-disubstitu[illegible] phenyl group, a 2,4-disubstituted phenyl group, a 3,4-disubstituted phenyl group and a 3,5-disubstituted phenyl group.

9. A use according to claim 8 wherein R^1 is substituted by two halo groups, the same or different, or by one halo group and one trifluoromethyl group.

10. A use according to claim 9 wherein R^1 is dichloro-substituted, difluoro-substituted, chloro-fluoro-substituted or fluoro-trifluoromethyl-substituted.

11. A use according to claim 1 wherein R^1 is selected from 3,4-dichlorophenyl, 3,4-difluorophenyl, 3-chloro-4-fluorophenyl, 4-chloro-3-fluorophenyl, 3-fluoro-4-(trifluoromethyl)phenyl, 4-fluoro-3-(trifluoromethyl)phenyl and 3-chloro-5-fluorophenyl.

12. A use according to any one of claims 1 to 11 wherein R^2 is alkyl.

13. A use according to any one of claims 1 to 12 wherein R^2 is C_{1-8} alkyl.

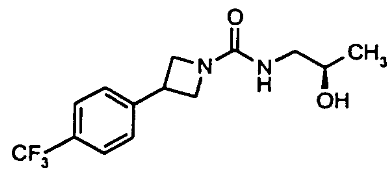
14. A use according to any one of claims 1 to 13 wherein R^2 is alkenyl, alkynyl, hydroxyalkyl or alkoxyalkyl.

15. A use according to any one of claims 1 to 13 wherein R^2 is unsubstituted saturated cyclic or acyclic hydrocarbyl.

16. A use according to any one of claims 1 to 13 wherein R^2 is propyl, 2-propenyl, 2-propynyl or 2-hydroxypropyl.

17. A use according to claim 1 wherein the compound of formula (I) is 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide or a pharmaceutically acceptable salt or prodrug thereof.

18. A use according to claim 1 wherein the compound of formula (I) is the (*R*) enantiomer of 3-(4-(trifluoromethyl)phenyl)-*N*-(2-hydroxypropyl)azetidine-1-carboxamide **(Ib)**



(Ib)

or a pharmaceutically acceptable salt or prodrug thereof, substantially free of its (*S*)-enantiomer.

19. A use according to any preceding claim wherein said medicament comprises a pharmaceutically acceptable carrier and as active ingredient an effective amount of compound (I).

20. A use according to claim 19 wherein said carrier comprises a cyclodextrin or an ether derivative thereof.

21. A use according to any preceding claim wherein the medicament further comprises a buffer system, an isotonizing agent and water.

22. Use according to any of preceding claim wherein the compound of formula (I) is in combination with one or more additional drugs useful in neuroprotection or in the treatment of cerebral ischaemia, central nervous system injury or eye diseases, the components being in the same formulation or in separate formulations for administration simultaneously or sequentially.

23. A method of neuroprotection comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 18, or a pharmaceutically acceptable salt or prodrug thereof.

24. A method of treatment of cerebral ischaemia, central nervous system injury or eye diseases comprising administration to a subject in need of such treatment an effective dose of a compound of formula (I) as set out in any of claims 1 to 18, or a pharmaceutically acceptable salt or prodrug thereof.

25. A method according to claim 23 or 24 wherein the compound of formula (I) is administered in the form as set out in any of claims 19, 20 or 21.

Figure 1

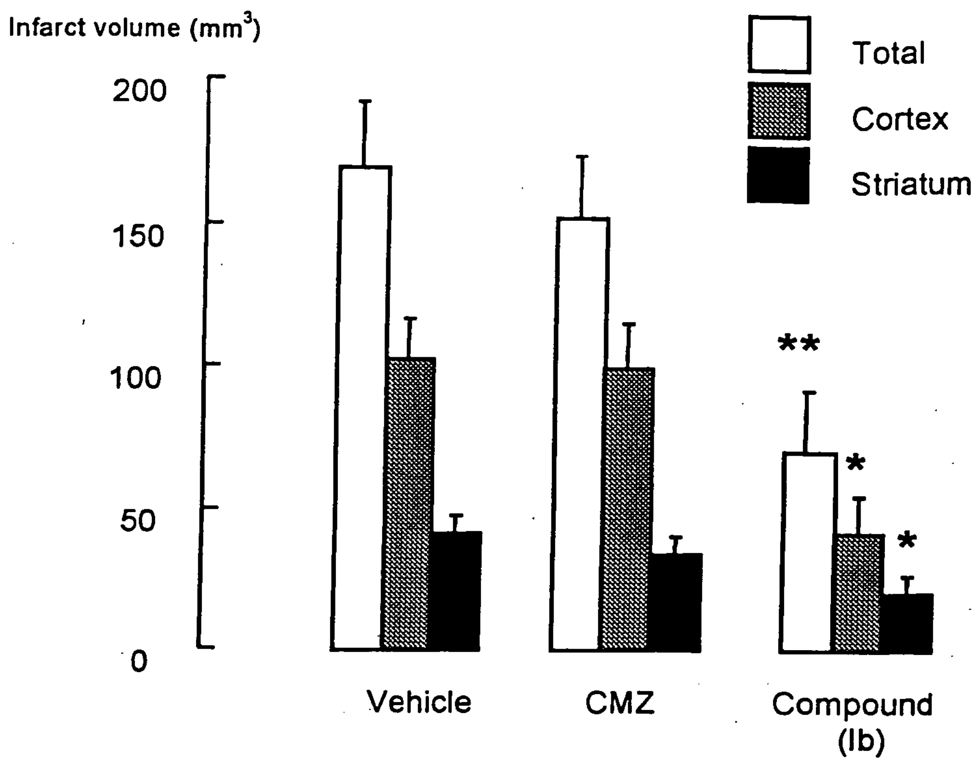
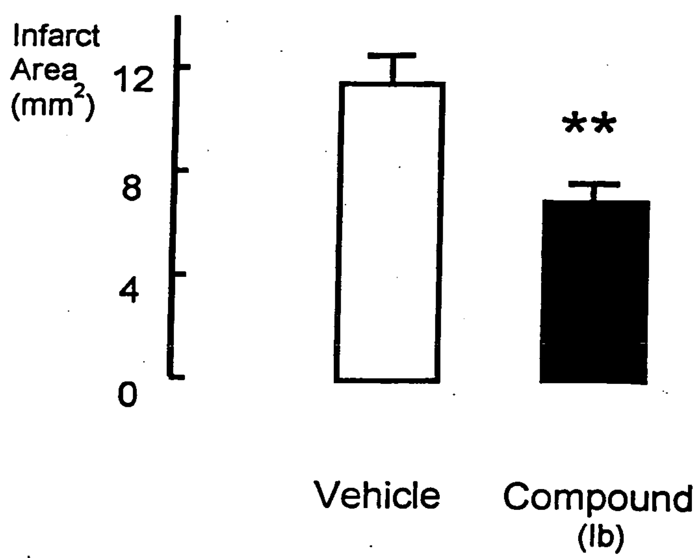


Figure 2



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